REMARKS

Specification

Applicant has amended the specification to remove the hyperlink found at page 3 (line 31) of the specification.

Non-obviousness

Claims 14, 16-18, 20, and 21 were rejected under 35 U.S.C. § 103(a) as unpatenable over US 2006/0068472 (hereafter "the '472 publication") entitled "Compositions to Ameliorate Protein Misfolding and Aggregation" in view of Madeo et al. ("A Caspase-Related Protease Regulates Apoptosis in Yeast, *Cell* 9:911-917, 2002; hereafter "Madeo").

The determination whether an invention would have been obvious under 35 U.S.C. § 103 is a legal conclusion based on underlying findings of fact. *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000). The factual determinations underpinning the legal conclusion of obviousness include 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). The Patent Office "bears the initial burden of presenting a prima facie case of unpatentability.... However, when a prima facie case is made, the burden shifts to the applicant to come forward with evidence and/or argument supporting patentability." *In re Glaug*, 283 F.3d 1335, 1338 (Fed. Cir. 2002). Evidence rebutting a *prima face* case of obviousness can include: "evidence of unexpected results" *Pfizer, Inc. v. Apotex*, Inc., 480 F.3d 1348, 1369 (Fed. Cir. 2007) and evidence "that the prior art teaches away from the claimed invention in any material respect," *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). When a patent applicant puts forth rebuttal evidence, the Office must consider that evidence. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (stating that "all evidence of nonobviousness must be considered when assessing patentability").

For the following reasons, the Office has failed to make a *prima facie* case of obviousness. In addition, even if it is believed that that Office did make a prima facie showing, applicant submits that the *prima facie* case is rebutted by surprising results discovered by the inventors that inhibition of expression of a caspase gene in yeast causes

the toxic effects of amyloidogenic proteins to be more pronounced.

The subject matter of the present claims relates to an engineered yeast cell and a method for identifying a compound which influences the toxic effect of amyloidogenic proteins in yeast. Representative claims 14 and 18, as originally filed, read as follows:

> 14. An engineered yeast cell, comprising a transgene encoding one or more amyloidogenic proteins or mutant(s) thereof, wherein said yeast strain is characterized in that it lacks a functional caspase gene.
>
> 18. A method for identifying a compound which influences the toxic effect of amyloidogenic proteins in yeast, said method comprising the steps of:
>
> a) providing an engineered yeast strain, comprising a transgene or a minigene encoding one or more amyloidogenic proteins or mutant(s) thereof, wherein said yeast strain is characterized in that it lacks a functional caspase gene,
>
> b) contacting the yeast strain obtained in step (a) with said compound, and
>
> c) determining the phenotypic effect of said compound on said yeast.

The Office, as noted above, has rejected these claims as being obvious over the '472 publication in view of Madeo. In concluding that claims 14, 16-18, 20, and 21 were obvious, the Office stated:

> *The ordinary skilled artisan, desiring to use a yeast strain lacking a functional capase gene, would have been motivated to combine the teachings of US 2006/0068472 teaching a yeast strain transformed with an amyloidogenic protein, and a screening method to identify agents that block the expression or alter the processing and aggregation of the toxic proteins with the teachings of Madeo et al teaching a yeast strain with disrupted YCA1* ***because US 2006/0068472 states that determining the mechanisms of toxicity of misfolded proteins remains the most important unresolved research problem for neurodegenerative diseases.*** *It would have been obvious to one of ordinary skill in the art to use a yeast strain lacking a functional capase* ***because Madeo et al. teach that the more simple yeast system may be better suited to resolve the order of some of the events in the apoptotic cascade.*** *Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. [emphasis added]*

No motivation existed in the art, much less in the '472 publication or Madeo, either alone or in combination, for one of skill in the art to engineer a yeast cell lacking a functional caspase gene in combination with expressing one or more amyloidogenic proteins or mutant(s) thereof. Moreover, even if there was motivation, which is not the case, applicant's surprising finding that yeast cells in which expression of a caspase gene is inhibited causes the toxic effects of amyloidogenic proteins to be more pronounced rebuts any prima facie case of obviousness.

The '472 publication and Madeo, alone or in combination, show no discernable reason for a skilled artisan to select a yeast cell lacking a caspase gene, and then engineer that cell to express one or more amyloidgenic proteins. Indeed, one passage, relied on by the Office to formulate the rejection, cited from '472 application in paragraph 245 on page 24 refers to therapeutic strategies:

> *Other **therapeutic strategies** include inhibiting the tendency of the protein to aggregate (either with itself or with other proteins), up-regulating heat shock proteins that protect against the toxic effects of misfolded protein, and blocking downstream effects, such as triggers of neuronal apoptosis. Overexpression of heat shock protein can reduce the toxicity of both mutant polyglutamine and mutant [alpha]-synuclein [...]and **caspase inhibition can reduce the toxicity** of both polyglutamine and mutant SOD [...], indicating that **therapeutic interventions of this type** may apply across multiple neurodegenerative diseases.* [emphasis added]

Indeed, this passage suggests a therapy where caspases are inhibited. Such therapy is performed by providing caspase inhibitors to a patient; not by inactivating a caspase gene such that a patient lacks a functional caspase. Moreover, the passage relied upon by the Office, alone or in combination with other passages of the '472 publication, does not suggest a yeast cell with amyloidogenic proteins wherein a caspase is inhibited, let alone a yeast cell where this inhibition is performed by deleting a caspase gene such that the yeast cell lacks a functional caspase.

The Office provides no reason as to why a skilled artisan would make particular modifications to either a yeast cell described in the '472 publication or to Madeo's yeast cell to achieve the claimed yeast cell. Apart from yeast cells, the '472 publication mentions many host cells ranging from prokaryotes such as Bacillus, Streptomyces, Pseudomonas, Salmonella, Serratia to eukaryotic cells such as fungi, insect cells, mammalian cells (such as

cells include HeLa cells, cells of fibroblast origin such as VERO or CHO-K1, or cells of lymphoid origin and their derivatives). The '472 publication also mentions plant cells and insect cells. The '472 publication even discusses worm cells as useful organisms for expressing proteins. In cases involving new cells, applicant asserts that it remains necessary to identify some reason that would have led a skilled artisan to modify a known cell in a particular manner to establish *prima facie* obviousness of a new claimed cell. This test for *prima facie* obviousness for cells such as the claimed engineered yeast cell is consistent with the legal principles enunciated in *KSR International Co. v. Teleflex Inc.*,127 S.Ct. 1727, 1731 (2007), where the Court reaffirmed the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). The application of the references relied upon by the Office for the *prima facie* case fail to meet this test.

Even if the Office established *prima facie* obviousness, which it has not, the Office's obviousness argument fails on a second ground. The '472 publication, at best, teaches that inhibiting caspases in a therapeutic context would reduce the toxicity of fragmented amyloidogenic proteins. Applicant surprisingly found that inhibition of expression of a caspase gene in yeast causes the toxic effects of amyloidogenic proteins to be more pronounced. This allowed the applicant to generate a model system in yeast which, as a result of the lack of a functional caspase gene, allows an easier phenotypic reading of the heterologously expressed amyloidogenic protein. This is advantageous both for the analysis of the mechanism of neurodegenerative diseases and for the screening of potential therapeutic agents or drug targets for use in the treatment of amyloidogenic neuropathies, as the effects of potential therapeutic agents are readily observed in this model system.

Such advantages are well described in the application. For example, the application at page 5 (lines 12-17) states:

> *More particularly, a yeast strain which as a result of a deletion mutation lacks a functional yeast caspase gene (yca1), was found to display an* ***increased sensitivity to the expression of amyloidogenic proteins****. Expression of such proteins in a mutant strain such as yca1, leads to a more severe*

inhibition of growth compared to wild type yeast strains that express a functional caspase gene. [emphasis added]

On page 5 (lines 24-30), the specification reads:

> *Thus according to a first aspect of the invention, yeast strains lacking a functional gene responsive to oxidative stress, expressing one or more amyloidogenic proteins or mutant derivatives thereof are used as a model for the cytotoxicity of these amyloidogenic proteins in mammals. More particularly yeast strains lacking a functional caspase gene, such as the mutant strains yca1 are provided,* ***which are particularly sensitive to the expression of amyloidogenic proteins****.* [emphasis added],

On page 22 (lines 17-19), the heading of Example 3 reads:

> *Expression of the gene encoding human alpha-synuclein in a yeast strain deleted for YCA1 :* ***alpha-synuclein hypersensitivity*** *in yca1 cells.* [emphasis added],

And on page 23 (lines 1-2) the specification reads:

> *Thus the absence of Yca1 activity* ***renders yeast cells hypersensitive*** *for intracellular produced alpha-synuclein.* [emphasis added].

A skilled person in search of a yeast strain where the toxicity of a heterologously expressed amyloidogenic protein is more pronounced would not be guided by the teaching of the '472 publication and, consequently, would not be motivated to combine the teachings of the '472 publication and Madeo because the '472 publication suggests reduced toxicity of amyloidogenic proteins when caspases are inhibited.

With respect to claim 18, applicant also points out that the '472 publication also states in paragraph 245:

> *Pharmaceutical screens are now underway to identify agents that block the expression or alter the processing and aggregation of the toxic proteins responsible for neurodegenerative disease, or mitigate the harmful effects of these proteins on neuronal function and survival.*

From the earlier above-cited passage of paragraph 245, the skilled person would understand that "caspase inhibition can reduce the toxicity of both polyglutamine and mutant SOD." In other words, upon reading the '472 publication, the outcome of performing a pharmaceutical screen with caspase inhibitors for identifying agents that alter processing of toxic proteins is already predicted; namely, being beneficial and reducing the toxicity. There is no teaching or

suggestion in the '472 publication that a screen should be performed under conditions where caspase function is inhibited, as is required in claim 18. There is also no teaching or suggestion in the '472 publication to perform a screen under conditions where the toxicity of an amyloidogenic protein is more pronounced to achieve a more sensitive readout to identify a compound.

The '472 publication and Madeo each fails to teach or suggest the use of yeast cells in screening methods where a yeast cell with a more pronounced toxicity of an amyloidogenic protein is used. The skilled artisan would therefore not be motivated to combine the teaching of the '472 publication with Madeo.

In view of applicant's aforementioned remarks, the rejections of claims 14, 16-18, 20, and 21 under 35 U.S.C. § 103(a) should be withdrawn.

Dependent claims 15 and 19 were also rejected on various grounds, also in view of the '472 publication and Madeo. In view of the above remarks relating to the '472 publication and Madeo, these rejections should be withdrawn as well.

CONCLUSIONS

Applicant submits that the claims are in condition for allowance, and such action is respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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